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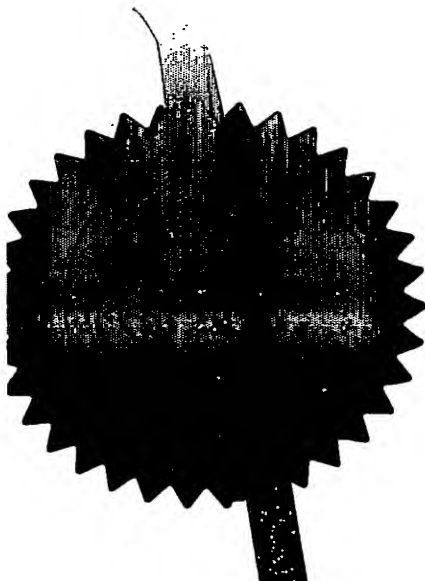
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JFR/JDS/CB60508P

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Glaxo Group Limited
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Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

00473587008

United Kingdom
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4. Title of the invention

Novel Compositions

5. Name of your agent (if you have one)

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Description	12
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We request the grant of a patent on the basis of this application

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Date 23-Sep-03

J F Reeves

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NOVEL COMPOSITIONS

The present invention relates to dentifrice compositions, in particular compositions comprising a fluoride source and a soluble calcium sequestering agent that is not an oxidising agent, for cleaning natural teeth and dentures. Such compositions show excellent cleaning properties whilst at the same time low abrasion characteristics.

Dentifrices have been used for more than 2000 years and the principle purpose of a dentifrice has always been the removal of surface deposits from the teeth. It is known that removal of surface deposits from the teeth can be achieved through the use of either a chemical or mechanical cleaning agent. An example of a chemical cleaning agent is a calcium-sequestering agent, for example a polyphosphate salt, such as tripolyphosphate, and the mechanical agents are the abrasive materials, e.g. precipitated silica or calcium carbonate. An example of an abrasive cleaning agent is amorphous hydrated silica. Bleaching agents are sometimes included in dentifrice compositions to decolourise tooth stains. This will not however remove the stain effectively and, furthermore, effective bleaching agents can damage the oral tissues and are difficult to formulate successfully. Hydrogen peroxide is a well-known bleaching agent but with peroxide-containing dentifrices the lifetime of peroxide in the oral cavity is very short. Human plaque contains a significant level of the peroxide-degrading enzyme catalase, which means that it is very difficult to maintain an effective level of peroxide on the tooth surface for sufficient time for stain to be bleached. More aggressive bleaching agents than peroxides however bring concerns over tissue damage.

Traditional dentifrice formulations contain a number of specific components for example abrasive agents, humectants, fluoride sources, binders, anti plaque agents, dyes, flavours, preservatives, water and other optional ingredients. Fluoride is an important aid to oral health, particularly for the health of the tooth's enamel. The effective removal of surface deposited stains is always associated with substantially abrasive formulations. It is however recognised that dentifrice compositions containing abrasive materials can damage the tooth surface so it is very important that a dentifrice formulation should provide effective cleaning without subjecting the tooth to excessive abrasion.

WO-A-95/17158 describes and claims a composition for reducing or removing surface deposited stains from natural teeth or dental prostheses comprising a dentally acceptable preparation comprising 5 to 15% by weight of a water soluble alkali metal

tripolyphosphate. All dentifrice formulation examples shown in WO-A-95/17158 include conventional dental abrasives, for example abrasive silica, the range 5-80 wt.% being disclosed.

- 5 The established method for determining the abrasivity of a dentifrice formulation is by measuring the Relative Dentine Abrasivity (RDA) (Hefferen, JJ. A laboratory method for measuring dentifrice abrasivity. *J. Dent. Res.* 55 563-573, 1976.). This assay measures loss of dentine due to extended brushing with a 25:40 w/w slurry of test material, e.g. toothpaste, from prepared samples of human dentine. The dentine
10 samples are irradiated to generate ^{32}P in the mineral. The assay measures radioactivity in the supernatant after brushing, relative to radioactivity liberated by brushing with a standard slurry of calcium pyrophosphate.

- Cleaning performance is closely linked with stain removal and can be measures in
15 various ways. There is a very useful published in-vitro stain removal (IVSR) assay (Layer TM, McConville PS and Wicks MA. Stain removal efficacy of whitening toothpastes – in vitro studies. *J. Dent. Res.* 79: 216 abstract 581, 2000) that is used in the present invention. This assay aims to maximise (as far as technically feasible) the relevance of the assay to the *in vivo* situation by using untreated naturally stained
20 bovine teeth as substrate. The teeth are brushed for an extended period with a 1:3 slurry of test toothpaste in water. Stain removal is quantified using a chromameter. Performance may be measured relative to a standard silica dentifrice containing 14% Zeodent 113 abrasive silica in a conventional base containing water, sorbitol, glycerin, PEG, flavour, SLS, sodium saccharin, Xanthum gum and sodium fluoride. IVSR is
25 also known as the natural extrinsic stain removal assay or NESR and is referred to as such in some publications.

Cleaning efficiency may therefore be described as the ratio of the IVSR to the RDA.

- 30 EP0 835 223 discloses an amorphous silica that has a low abrasivity value which, when incorporated into a dentifrice composition maintains good cleaning characteristics. This publication however only considers the abrasive silica as the cleaning material of the composition and describes the amorphous silica in terms of its physical properties. Accordingly 0 835 223B claims an amorphous silica
35 characterized by: an RDA value of between 30 and 70, an oil absorption capacity of between 100 and 155cm³/100g, and a BET surface area of up to 200m²/g.

From the literature it appears that many formulations that are dependent for their cleaning properties upon their abrasive content are described and claimed in terms of the physical properties of the abrasive material. For example EP-A-0 396 460 describes in Example 1 an amorphous silica in terms of BET surface area, oil uptake,
5 pore volume, pH, refractive index and translucence.

EP-A-0 002 184 discloses the use of a sodium polyphosphate in fine granulate form for tooth cleaning, either by itself or in combination with a commercial toothpaste formulation, referring to the abrasive effect of the sodium polyphosphate and
10 intensification of tooth cleaning by this material without damaging the substance of the teeth.

A highly effective dentifrice formulation without the traditional amounts of abrasive material has not been disclosed or described in the prior art. By the term "highly
15 effective dentifrice" is meant to refer to a dentifrice that satisfactorily removes stain from natural teeth or dentures whilst at the same time will not damage the dentine or enamel due to excessive abrasivity.

It is an object of the present invention to provide a dentifrice composition, for natural
20 teeth and dentures, which addresses one or more of the problems mentioned above.

Accordingly, the present invention provides a dentifrice composition comprising a soluble calcium sequestering agent that is not an oxidising agent, wherein the composition has an RDA value of below 30 and an IVSR value greater than 50%, and
25 an orally acceptable vehicle.

Preferably the composition is a non-gel toothpaste being a viscous extrudable fluid which can be provided in a collapsible container e.g. a tube or a pump and extruded therefrom onto a toothbrush for use.
30

Preferably the RDA value is below 25, preferably below 20, and most preferably as low as possible, e.g. so that the composition is substantially non-abrasive. Preferably the IVSR value is up to 250, preferably 200 and more preferably greater than 100, for example being in the range 75-150, e.g. 75-120.
35

The soluble calcium-sequestering agent may be a calcium-chelating agent. Suitable soluble calcium sequestering agents include:

Polyphosphate salts (also known as condensed phosphate salts) according to formula: $M_{n+2}^+[P_nO_{3n+1}]$, where $n > 1$, M = alkali metal, hydrogen ion or ammonium ion.

5 Pyrophosphates, for example alkali metal salts of pyrophosphate, and pyrophosphate salts in which hydrogen ion and/or ammonium ion may partially substitute for the alkali metal ions. Examples of these are:

$Na_4P_2O_7$	Tetrasodium pyrophosphate
$Na_2H_2P_2O_7$	Disodium dihydrogen pyrophosphate
$K_4P_2O_7$	Tetrapotassium pyrophosphate
10 $K_2H_2P_2O_7$	Dipotassium dihydrogen pyrophosphate
$Na_2K_2P_2O_7$	Dipotassium disodium pyrophosphate

15 Tripolyphosphates, for example alkali and mixed alkali metal salts of tripolyphosphate, and tripolyphosphate salts in which hydrogen ion and/or ammonium ion may partially substitute for the alkali metal ions. Examples are:

$Na_5P_3O_{10}$	Pentasodium tripolyphosphate
$K_5P_3O_{10}$	Pentapotassium tripolyphosphate

20 Higher polyphosphate salts such as sodium and potassium tetrphosphates, and hexametaphosphate salts, also known as 'glassy phosphates' or 'polypyrophosphates'

25 Carboxylates, for example: alkali metal citrate salts, which may be partially substituted with hydrogen ion or ammonium ion, alkali metal acetate, lactate, tartrate and malate salts, which may be partially substituted with hydrogen ion or ammonium ion. Alkali metal salts of ethylenediaminetetraacetic acid (EDTA), which may be partially substituted with hydrogen ion or ammonium ion and editronic acid.

30 Two or more of the above-mentioned calcium sequestering agents may be used in combination in the composition.

A preferred soluble calcium-sequestering agent is pentasodium tripolyphosphate, often referred to as sodium tripolyphosphate.

35 In use during toothbrushing the calcium-sequestering agent normally dissolves and so provides a cleaning effect in its dissolved state. The composition of the invention may be so formulated that the calcium-sequestering agent is in a dissolved state during use in toothbrushing, or in an aqueous vehicle.

The soluble calcium-sequestering agent, such as sodium tripolyphosphate, may be present in a proportion 1-20wt %, preferably 2-15wt%, more preferably 5-15wt% of the dentifrice composition. By using a proportion of the calcium-sequestering agent in the composition below the solubility limit thereof a gel or liquid compositions may be provided in which the calcium sequestering agent is in solution, so that the gel or liquid may include no undissolved solid particles, and may be a clear gel or liquid.

The composition may include a fluoride ion source. Fluoride ion may stabilise polyphosphates in the mouth. For a composition for use in cleaning natural teeth the inclusion of a fluoride ion source is also desirable because of its caries protection activity, but for a composition for use in cleaning artificial dentures such activity is not necessary. The fluoride ion source may be provided by an alkali metal fluoride, preferably sodium fluoride, an alkali metal monofluorophosphate, stannous fluoride and the like. Preferably, however, the fluoride ion source is an alkali metal fluoride, most preferably sodium fluoride. The fluoride ion source serves in a known manner for caries protection. Preferably, the fluoride ion source will be used in an amount to provide an anti-caries effective amount and a phosphatase enzyme inhibiting amount, such as an amount sufficient to provide from about 25 ppm to about 3500 ppm, preferably about 1100 ppm, as fluoride ion. For example the formulation may contain 0.1 – 0.5 wt % of an alkali metal fluoride such as sodium fluoride.

Preferably the pH of the composition is from about 6 to 10.5, more preferably from about 7 to about 9.5. Typically the composition may contain up to 0.5 wt.% of sodium hydroxide to provide a suitable pH.

In compositions of the present invention which are usable in the manner of conventional toothpastes, i.e. which can be extruded onto a toothbrush, the orally acceptable vehicle may be of a generally conventional composition e.g. comprising a thickening agent, a binding agent and a humectant. Preferred binding agents include for example natural and synthetic gums such as xanthan gums, carageenans, alginates, cellulose ethers and esters. Preferred humectants include glycerin, sorbitol, propylene glycol and polyethylene glycol. A preferred humectant system consists of glycerin, sorbitol and polyethylene glycol.

In addition, the orally acceptable vehicle may optionally comprise one or more surfactant, sweetening agent, flavouring agent, anticaries agent (in addition to the fluoride ion source), anti-plaque agent, anti-bacterial agent such as triclosan or cetyl pyridinium chloride, tooth desensitizing agent, colouring agents and pigment. Useful

surfactants include the water-soluble salts of alkyl sulphates having from 10 to 18 carbon atoms in the alkyl moiety, such as sodium lauryl sulphate, but other anionic surfactants as well as non-ionic, zwitterionic, cationic and amphoteric surfactants may also be used.

5

If an aqueous orally acceptable vehicle is employed, a toothpaste composition of the present invention suitably contains from about 10 to about 80 wt % humectant such as sorbitol, glycerin, polyethylene glycol or xylitol; from about 0.25 to about 5 wt % detergent; from 0 to about 2 wt % sweetener and flavouring agents; together with
10 water and an effective amount of binding and thickening agents, such as from about 0.1 to about 15 wt %, to provide the toothpaste of the invention with the desired stability and flow characteristics.

15

It is preferred to use a thickening silica as the thickening agent. So called "thickening silicas" are known silicas which have relatively little abrasive effect compared with known abrasive silicas such as Zeodent 113™ available from J.M. Huber Corporation, but provide a thickening effect on the composition. Suitable thickening silicas are known and include those marketed by Degussa AG under the trade name SIDENT®, e.g. SIDENT 22S®, and by Grace-Davison Chemical Division under the trade name
20 SYLOBLANC®, e.g. SYLOBLANC 15®, respectively. For example the composition may contain up to ca. 20wt % of a thickening silica, typically 5-15 wt %.

25

The composition of the invention may contain an abrasive material, for example known types of "abrasive silica" commonly used in toothpaste compositions e.g. Zeodent 113™ as mentioned above. However to achieve the RDA below 30 it is preferred to include as little of this type of abrasive material as possible, preferably less than 5 wt.%, more preferably less than 3wt%, more preferably less than 2 wt.% abrasive, more preferably less than 1 wt.% abrasive, most preferably 0 wt.% abrasive material, in addition to any mild abrasive effect produced by other solid particles in
30 the composition, e.g. undissolved calcium sequestering agent and e.g. any thickening silica present. For the purposes of this invention an abrasive material may be defined as a material having a RDA of 30 or above. Larger amounts of silica may be incorporated, more typical of abrasive silica incorporation levels in toothpastes (up to e.g. 25%), if that silica has an RDA below 30.

35

Regarding the RDA values given in the preceding paragraph, it should be noted that the slurry conditions used to determine the abrasivity of an abrasive raw material differ from those used to determine the abrasivity of a formulated toothpaste. The

slurry conditions for a raw material are 10g abrasive plus 50ml of a 0.5% carboxymethyl cellulose slurry in 10% glycerin, whereas the slurry conditions for a formulated toothpaste are 25g toothpaste plus 40ml water. This means that a silica abrasive is generally present at a higher concentration when that silica is tested as a raw material than when that silica is tested after formulation into a toothpaste. Care should therefore be taken when comparing RDA figures for abrasives as raw materials with RDA figures for toothpastes.

Therefore a preferred dentifrice composition of this invention comprises a soluble calcium sequestering agent that is not an oxidising agent, wherein the composition has an RDA value of below 30 and an IVSR value greater than 50%, and an orally acceptable vehicle, wherein the calcium sequestering agent is present in a proportion 1-20wt %, preferably 5-10 wt % of the composition, with 0 - 5 %, preferably 0 % of an abrasive, typically an abrasive silica.

The dentifrice composition may be presented as either a single or dual phase composition. Suitably the composition is in the form of a conventional toothpaste-type composition that can be squeezed from a collapsible tube.

Toothpaste-type compositions according to the present invention may be prepared by admixing according to conventional practice the calcium sequestering agent, and the fluoride ion source if present, with the orally acceptable dental vehicle, which may be anhydrous but is preferably an aqueous orally acceptable dental vehicle, to form a storage-stable semi-solid extrudable material useful as a dentifrice.

The composition of the invention will now be described by way of non-limiting examples only.

5 **Table 1. Examples of the present invention using different calcium sequestering systems**

Ingredient	1	2	3	4	5	6
Glycerin, 98% min	11.20	11.20	11.20	11.20	11.20	11.20
Sorbitol, 70% soln.	29.11	29.11	29.11	29.11	29.11	29.11
Peg 6	3.00	3.00	3.00	3.00	3.00	3.00
Xanthan gum	0.70	0.70	0.70	0.70	0.70	0.70
Flavour	1.00	1.00	1.00	1.00	1.00	1.00
Soluble saccharin	0.21	0.21	0.21	0.21	0.21	0.21
Sodium lauryl sulphate	1.15	1.15	1.15	1.15	1.15	1.15
Sodium tripolyphosphate	10.00	0.00	10.00	0.00	4.00	0.00
Tetra sodium pyrophosphate	0.00	1.80	0.00	0.00	0.90	0.00
Tetrapotassium pyrophosphate	0.00	4.00	0.00	0.00	2.00	0.00
Sodium trimetaphosphate	0.00	0.00	5.00	0.00	0.00	0.00
Sodium Hexametaphosphate	0.00	0.00	0.00	7.00	0.00	0.00
Trisodium citrate	0.00	0.00	0.00	0.00	0.00	5.00
Sodium hydroxide	0.00	0.25	0.25	0.25	0.25	0.00
Sodium fluoride	0.24	0.24	0.24	0.24	0.24	0.24
Titanium dioxide	1.45	1.00	1.00	1.00	1.00	1.00
Abrasive silica Zeodent 113	0.00	0.00	0.00	0.00	0.00	0.00
Thickening silica	13.50	13.50	13.50	13.50	13.50	13.50
De-ionised water	28.44	32.84	23.64	31.64	31.74	33.89
Total	100.00	100.00	100.00	100.00	100.00	100.00

Various embodiments of the invention may be prepared.

- 10 Example 1 is a formulation in which the calcium-sequestering chemical cleaning system is sodium tripolyphosphate (STP). Thickening silica is increased to account for the lower level of solids in the formulation, and sodium hydroxide is added to increase the pH and thereby increase the stability of the polyphosphate component. Other polyphosphate may be used as chemical cleaning agent and/or anticaries agent.

Example 2 is an equivalent formulation using mixed pyrophosphate salts instead of STP.

Example 3 uses trimetaphosphate, and example 4 sodium hexametaphosphate.

5

Example 5 shows that mixed calcium-sequestration systems may be used, this embodiment combining different polyphosphate salts.

10

Example 6 uses an effective amount of a polycarboxylate, trisodium citrate, as a calcium-sequestering agent.

Table 2. Examples of the present invention with different product forms

Ingredient	Example					
	7	8	9	10	11	12
Glycerin, 98% min	11.20	0.00	13.00	11.20	11.20	10.00
Sorbitol, 70% soln.	29.11	65.00	35.00	29.11	29.11	26.00
Peg 6	3.00	3.00	3.00	3.00	3.00	3.00
Xanthan gum	1.50	0.50	1.80	0.70	0.40	0.70
Flavour	1.00	1.00	1.00	1.00	1.00	1.00
Soluble saccharin	0.21	0.15	0.21	0.21	0.21	0.21
Sodium lauryl sulphate	1.15	1.15	1.15	1.15	1.15	0.00
Tegobetaine	0.00	0.00	0.00	0.00	0.00	2.00
Sodium tripolyphosphate	10.00	1.00	10.00	10.00	10.00	10.00
Tetra sodium pyrophosphate	0.00	0.90	0.00	0.00	0.00	0.00
Tetrapotassium pyrophosphate	0.00	2.00	0.00	0.00	0.00	0.00
Trisodium citrate	0.00	1.00	0.00	0.00	0.00	0.00
Sodium hydroxide	0.00	0.30	0.00	0.30	0.00	0.00
Sodium fluoride	0.24	0.24	0.24	0.24	0.24	0.24
Titanium dioxide	1.00	0.00	1.00	1.00	1.00	1.00
Abrasive silica Zeodent 113	0.00	0.00	0.00	2.00	0.00	0.00
Polypropylene beads	0.00	0.00	0.00	0.00	0.00	15.00
Thickening silica	6.50	11.00	0.00	13.50	9.00	6.50
De-ionised water	35.09	12.76	33.60	26.59	33.69	24.35
Total	100.00	100.00	100.00	100.00	100.00	100.00

15

Table 2 provides further examples incorporating the invention into different product types.

Example 7 shows that the thickening silica need not be increased to compensate for the lack of abrasive silica. In this example the level of thickening silica is the same as

in the formulation containing the normal level of abrasive (6.5%). However, the gum level is raised to maintain adequate viscosity.

Example 8 shows that clear gels may be prepared according to the present invention.

5 In this case it is important to keep the level of certain calcium-sequestering salts below their limit of solubility, so a combination of different salts is used. This example also shows that polyphosphates may be combined with carboxylate calcium-sequestering agents.

10 Example 9 shows that silica may be omitted from the formulation altogether whilst still maintaining good cleaning from calcium-sequestering agents.

Example 10 shows that low levels of abrasive silica may be included in the formulations of the present invention. Provided the final RDA value is below 30, it is
15 found that the remarkable cleaning efficiency of the invention is retained.

Example 11 shows a low-viscosity liquid toothpaste formulation.

Example 12 shows a formulation with zwitterionic surfactant, which may be
20 employed to minimise any possible irritation to oral tissues.

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30

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Table 3. Examples of the present invention with different therapeutic activities

Ingredient	Example number				
	13	14	15	16	17
Glycerin, 98% min	11.20	0.00	0.00	11.20	22.00
Sorbitol, 70% soln.	29.11	45.00	29.11	29.11	28.00
Xylitol	0.00	0.00	10.00	0.00	0.00
Peg 6	3.00	2.00	3.00	3.00	2.50
Xanthan gum	0.70	0.90	0.70	0.70	0.25
Flavour	0.80	1.20	1.00	1.00	1.70
Soluble saccharin	0.21	0.21	0.21	0.21	0.30
Sodium lauryl sulphate	0.80	1.50	1.15	0.00	1.50
Triclosan	0.00	0.30	0.00	0.00	0.00
F127*	0.00	0.00	0.00	2.00	0.00
Sodium tripolyphosphate	5.00	10.00	4.00	10.00	5.00
Tetra sodium pyrophosphate	0.00	0.00	1.80	0.00	0.00
Casein phosphopeptide	0.00	0.00	2.00	0.00	0.00
Tetrapotassium pyrophosphate	0.00	0.00	4.00	0.00	0.00
Potassium nitrate	5.00	0.00	0.00	0.00	0.00
Lactoperoxidase	0.00	0.00	0.00	0.20	0.00
Glucose oxidase	0.00	0.00	0.00	0.20	0.00
Sodium hydroxide	0.35	0.00	0.00	0.00	0.00
Sodium fluoride	0.24	0.24	0.55	0.24	0.24
Titanium dioxide	1.00	1.00	1.00	1.00	0.00
Thickening silica	13.50	12.50	13.50	13.50	5.50
Butane	0.00	0.00	0.00	0.00	3.00
Dimethyl ether	0.00	0.00	0.00	0.00	2.00
De-ionised water	29.09	25.15	27.98	27.64	28.01
Total	100.00	100.00	100.00	100.00	100.00

*Ethylene oxide-propylene oxide block copolymer.

Example 13 is a formulation according to the present invention containing therapeutic amounts of potassium nitrate to relieve the pain of sensitive teeth.

5

Example 14 is an anti-gingivitis formulation according to the present invention based on inclusion of Triclosan.

Example 15 is a formulation according to the present invention designed to provide highly effective anticavity protection, containing 2500ppm fluoride, xylitol and casein phosphopeptide.

10

Example 16 is a formulation according to the present invention containing active enzymes to control plaque bacteria, using non-ionic surfactant to maximise the stability of the biological molecules.

15

Example 17 is a formulation according to the present invention suitable for dispensing from a pressurised aerosol container.

Cleaning efficacy and abrasivity testing.

The cleaning efficacy of a formulation given in Example 1 was tested. This formulation was tested against a standard abrasive-containing toothpaste formulation according to control example 1, with water as a negative control, using the method of Layer *et al.* The formulations were also sent to the Oral Health Research Institute, University of Indiana for RDA testing. The values for the stain removal and abrasivity are given in Table 4 below:

Table 4. IVSR cleaning and abrasivity data for formulation Example 1

Formulation	Silica level	STP level	RDA	IVSR cleaning
Example 1 (abrasive-containing control)	14	0	50.69 ± 2.97	100 ± 9.42
Example 2	0	10	9.99 ± 0.47	115.51 ± 10.78
Water	-	-	-	-10.82 ± 14.26

As can be seen from Table 4, the abrasivity of the formulation according to the present invention Example 1, was extremely low (RDA=9.99). The control paste gave an abrasivity in the expected range for formulations of this type. However, the cleaning value of the prototype formulation was 115% of the abrasive-containing control, demonstrating extremely effective cleaning performance. The table also shows that brushing with water does not remove stain from this substrate.

CLAIMS

- 5 1. A dentifrice composition comprising a soluble calcium sequestering agent that is not an oxidising agent, wherein the composition has an RDA value of below 30 and an IVSR value greater than 50%, and an orally acceptable vehicle.
2. A dentifrice composition according to claim 1, wherein the soluble calcium
10 sequestering agent is a calcium-chelating agent.
3. A dentifrice composition according to claim 2, wherein the calcium-chelating agent is a polyphosphate or pyrophosphate salt.
- 15 4. A dentifrice composition according to claim 3, wherein the IVSR value is measured relative to a standard silica dentifrice containing 14% Zeodent 113 abrasive silica in a conventional base containing water, sorbitol, glycerin, PEG, flavour, SLS, sodium saccharin, Xanthum gum and sodium fluoride.
- 20 5. A method of cleaning natural teeth or dentures using a dentifrice composition according to any one of the above claims.